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**Ethical and Regulatory Challenges  
with Autologous Adult Stem Cells:  
A Comparative Review of International Regulations**

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## Ethical and Regulatory Challenges with Autologous Adult Stem Cells: A Comparative Review of International Regulations

### INTRODUCTION

Over the last decade, the use of human cell and tissue-based products (CTPs) in new and innovative therapies has drawn increasing interest from healthcare providers, researchers, patients, and regulators, internationally. However, despite there being few accepted clinical uses,<sup>1</sup> CTPs are increasingly being prescribed for conditions that have not been demonstrated as safe or effective in clinical trials. In particular, autologous adult stem cells (ASCs) are being offered directly to patients, typically over the Internet, for a wide range of diseases and conditions for which there is insufficient evidence that demonstrates their safety and efficacy.<sup>2</sup> While evidence has emerged in recent years to reduce initial safety fears about the tumour-forming properties of ASCs, clinical data that supports the efficacy of these products for many indications has been either limited to early Phase I/II trials, or in some cases, non-existent.<sup>3</sup>

Until recently, these practices were utilized mainly by patients travelling from wealthy nations to low-to-middle income countries, or so-called 'stem cell tourism'.<sup>4</sup> These countries, including China, Thailand, and India,<sup>5</sup> were assumed to foster stem cell clinics because they lacked the necessary regulatory infrastructure to monitor and control the practices of clinics and healthcare institutions operating within their jurisdiction.<sup>6</sup> This picture is, however, no longer adequate, as autologous ASCs are increasingly being offered in wealthy countries, such as the United States, Japan and Australia.<sup>7</sup> This means both that patients need no longer travel long distances to access 'unproven' cellular therapies and that the global escalation of these practices cannot be simply explained as a matter of poor or weak regulation in emerging economies.

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<sup>1</sup> George Q Daley, "The Promise and Perils of Stem Cell Therapeutics," *Cell stem cell* 10, no. 6 (2012).

<sup>2</sup> Alan C. Regenberg et al., "Medicine on the Fringe: Stem Cell-Based Interventions in Advance of Evidence," *Stem Cells* 27, no. 9 (2009); Darren Lau et al., "Stem Cell Clinics Online: The Direct-to-Consumer Portrayal of Stem Cell Medicine," *Cell Stem Cell* 3, no. 6 (2008).

<sup>3</sup> Carl Power and John E Rasko, "Promises and Challenges of Stem Cell Research for Regenerative Medicine," *Annals of Internal Medicine* 155, no. 10 (2011).

<sup>4</sup> Use of this label to describe the complexity of marketing stem cells direct to patients has been criticized elsewhere. Tamra Lysaght and Doug Sipp, "Dislodging the Direct to Consumer Marketing of Stem Cell-Based Interventions from Medical Tourism," in *Bodies across Borders: The Global Circulation of Body Parts, Medical Tourists and Professionals*, ed. Brownwyn Parry, et al. (Ashgate Press, 2014).

<sup>5</sup> Regenberg et al., "Medicine on the Fringe: Stem Cell-Based Interventions in Advance of Evidence."; Lau et al., "Stem Cell Clinics Online: The Direct-to-Consumer Portrayal of Stem Cell Medicine."

<sup>6</sup> Sorapop Kiatpongsan and Douglas Sipp, "Offshore Stem Cell Treatments," *Nature Reports Stem Cells* (2008).

<sup>7</sup> Tamra Lysaght et al., "Oversight for Clinical Uses of Autologous Adult Stem Cells: Lessons from International Regulations," *Cell Stem Cell* 13, no. 6 (2013).

In a study funded by the Ethical and Social Research Council in the United Kingdom, Petra and Sleeboom-Falkner describe how disparities in regulatory systems across geographical contexts are being exploited by what they term as 'bionetworks'<sup>8</sup>. These networks are represented by loosely organized transnational relationships between physicians, science entrepreneurs, researchers and patients, who operate mostly, although not exclusively, within the private healthcare sector.<sup>9</sup> They work in part by exploiting differences and inequalities in the provision of healthcare, standards of wealth, capacity to conduct scientific research, and regulatory infrastructure between rich and poor(er) countries. While this study provides some evidence of bionetworks extending out of Asia and into the highly protected markets of the so-called 'West', most notably through patient recruitment,<sup>10</sup> their infiltration into high income countries with lucrative domestic markets for novel therapeutics has not been uniform nor has it been essential for the global proliferation of clinics offering autologous ASCs outside clinical trials.

The global reach of bionetworks is most clearly visible in the recent events in Texas, where the Governor Rick Perry was administered with autologous ASCs processed using technology imported from the Seoul-based company formerly known as RNL Bio (it is now operating as K-STEMCELL).<sup>11</sup> This intervention followed a similar procedure that had been carried out on Perry's physician at a clinic associated with RNL Bio in Japan,<sup>12</sup> where more than 20 clinics are reportedly offering autologous ASCs.<sup>13</sup> Yet, in Australia, where a sharp increase in such clinics has occurred following the introduction of a new regulatory framework for CTPs,<sup>14</sup> the connections with bionetworks in Asia or elsewhere are less visible. Furthermore, other countries such as Singapore, Canada and the United Kingdom, have been relatively successful in controlling the use of autologous ASCs within their borders. Hence, there are likely differences in regulatory systems amongst *wealthy nations* with similar standards in healthcare, scientific investment and economic structure that may be encouraging or discouraging the provision of autologous ASCs to patients outside clinical trials.

This paper examines the regulatory systems of five geographically diverse but socio-economically comparable countries with the aim of identifying similarities and differences in how novel uses of CTPs are regulated and governed within clinical contexts. We follow this examination with a discussion about the strengths and weaknesses of these approaches and suggest ways in which international governance may better achieve a balance between the need to protect vulnerable patient populations and the desire to enable scientific and clinical innovation.

<sup>8</sup> Prasanna Kumar Patra and Margaret Sleeboom-Faulkner, "Bionetworking: Experimental Stem Cell Therapy and Patient Recruitment in India," *Anthropology & Medicine* 16, no. 2 (2009).

<sup>9</sup> Margaret Sleeboom-Faulkner and Prasanna Kumar Patra, "Experimental Stem Cell Therapy: Biohierarchies and Bionetworking in Japan and India," *Social Studies of Science* 41, no. 5 (2011).

<sup>10</sup> Patra and Sleeboom-Faulkner, "Bionetworking: Experimental Stem Cell Therapy and Patient Recruitment in India."

<sup>11</sup> Tamra Lysaght et al., "Global Bionetworks and Challenges in Regulating Autologous Adult Stem Cells," *American Journal of Medicine* 126, no. 11 (2013).

<sup>12</sup> Susan Berfield, "Stem Cell Showdown: Celltex Vs. The Fda," *Businessweek* (2013), <http://www.businessweek.com/articles/2013-01-03/stem-cell-showdown-celltex-vs-dot-the-fda>

<sup>13</sup> Akira Akabayashi and Misao Fujita, "The Present and Future of Stem Cell Therapy in Japan" (paper presented at the Ethics for the Future of Life: Proceedings of the 2012 Uehiro-Carnegie-Oxford Ethics Conference, 2012).

<sup>14</sup> Megan Munsie and Martin Pera, "Regulatory Loophole Enables Unproven Autologous Cell Therapies to Thrive in Australia," *Stem Cells and Development* in print (2014).

## COMPARATIVE REVIEW OF INTERNATIONAL REGULATORY APPROACHES TO CTPs

The five countries selected for the comparative review – Australia, Japan, Singapore, the UK, and the USA – were chosen from the extant literature because of their comparability across key socioeconomic and health indicators. They are all structured as capital markets and are among the 46 countries classified by the World Bank as high-income economies.<sup>15</sup> They each spend between 1.7 and 3.4% of gross domestic product a year in research and development<sup>16</sup> and have comparably high capacities for scientific research.<sup>17</sup> While different healthcare systems are in place, the standards of healthcare offered to patients are relatively stable across these jurisdictions.<sup>18</sup> These countries have also invested heavily in biomedicine and medical biotechnologies, including regenerative medicines based on stem cells and other CTPs.

To support these investments, these countries have all established regulatory infrastructure to enable the protection of intellectual property rights and govern research involving human subjects. Regulations for human subject research in each country are based on internationally-accepted standards initially set in the Nuremberg Code and later adopted by the World Medical Association (WMA) in the Declaration of Helsinki<sup>19</sup> and the Council for International Organizations of Medical Sciences (CIOMS) for the International Ethical Guidelines for Biomedical Research Involving Human Subjects.<sup>20</sup> These standards outline basic imperatives for informed consent, voluntariness, privacy, confidentiality and independent oversight from an Institutional Review Board (IRB) or an equivalent body. Most have also established frameworks for research involving human stem cells and tissues. Specific laws, regulations and guidelines adopted in each country for human subject and stem cell research are extensive, of which some are shown in Table 1.

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<sup>15</sup> World Bank (2012), List of Economies, Available at [http://data.worldbank.org/about/country-classifications/country-and-lending-groups#High\\_income](http://data.worldbank.org/about/country-classifications/country-and-lending-groups#High_income) (Accessed 17 June 2013).

<sup>16</sup> World Bank (2008), Research and development expenditure (% of GDP), Available at <http://data.worldbank.org/indicator/GB.XPD.RSDV.GD.ZS> (Accessed 17 June 2013).

<sup>17</sup> IMH (2013), World Competitiveness Online, Available at <https://www-worldcompetitiveness-com> (Accessed 17 June 2013).

<sup>18</sup> IMH (2013), World Competitiveness Online, Available at <https://www-worldcompetitiveness-com> (Accessed 17 June 2013).

<sup>19</sup> Available at <http://www.wma.net/en/30publications/10policies/b3/> (Accessed 17 June 2013).

<sup>20</sup> Available at [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf) (Accessed 17 June 2013).

**Table 1: Regulatory Mechanisms for Human Subject and Stem Cell Research**

<b>Jurisdiction</b>	<b>Administrating Body</b>	<b>Laws &amp; Regulations</b>	<b>Guidelines</b>
<b>United States</b>	Environmental Protection Agency, Program in Human Research Ethics	Title 40 Code of Federal Regulations Part 26 Subpart A: The Common Rule	
	Food and Drug Administration, Center for Biologics Evaluation and Research	Research on Transplantation of Fetal Tissue. Public Law 103-43	Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products. October 14, 1993. 58 FR 53248
	National Academy of Sciences		Guidelines for Human Embryonic Stem Cell Research (2005, amended 2007, 2008 & 2010)
	National Institutes of Health		Guidelines on Human Stem Cell Research (2009) Human Embryonic Stem Cell Registry (2009)
<b>United Kingdom</b>	European Commission	Directive 2004/23/EC on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage, and Distribution of Human Tissues and Cells	
	Council of Europe, Bioethics Division	Convention on Human Rights and Biomedicine (Convention of Oviedo), Articles 18, ETS No. 164 (1997) Additional Protocol on Prohibition of Human Cloning, ETS No. 168 (1998):	Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research, CETS No. 195 (2005) Additional Protocol Concerning Biomedical Research, CETS No. 195
	European Group on Ethics in Science and New Technologies		Ethical Aspects of Human Tissue Banking (1998)
	Department of Health		The Use of Human Organs and Tissue: An Interim Statement (2003)
	Economic and Social Research Council		Research Ethics Framework
	Human Fertilisation and Embryology Authority	Human Fertilisation and Embryology Act (1990) Human Fertilisation and Embryology (Research Purposes) Regulation (2001)	

<b>Australia</b>	National Health and Medical Research Council, Australian	National Health and Medical Research Council Act (1992) and Regulations (2006)	National Statement on Ethical Conduct in Human Research (2007)
	Health Ethics Committee and the Embryo Research Licensing Committee	Prohibition of Human Cloning Act (2008) Research Involving Human Embryos Regulations (2003) Research Involving Human Embryos Act (2008)	Australian Code for the Responsible Conduct of Research (2007) Ethical Guidelines on the Use of Assisted Reproductive Technology in Clinical Practice and Research (2007)
<b>Japan</b>	Ministry of Health, Labor, and Welfare	Act on Regulation of Human Cloning Techniques (2000) Rules for Enforcement of Act on Regulation of Human Cloning Techniques (2009)	Ethical Guidelines for Clinical Research (2008) On Research and Development Utilizing Human Tissues Removed by Surgery and Other Procedures (1998) Guidelines for Clinical Research Using Human Stem Cells (2006)
	Ministry of Education, Culture, Sports, Science, and Technology		Guidelines for Handling of a Specified Embryo (2009) Guidelines for Derivation and Distribution of Human Embryonic Stem Cells (2009) Guidelines for Utilization of Human Embryonic Stem Cells (2009)
<b>Singapore</b>	Ministry of Health	Medical (Therapy, Education, and Research) Act (1973) Human Cloning and Other Prohibited Practices Act (2004)	Governance Framework for Human Biomedical Research (2007) Code of Ethical Practice in Human Biomedical Research (2009)
	Ministry of Health National Medical Ethics Committee		Ethical Guidelines on Research Involving Human Subjects
	Bioethics Advisory Committee		Report on Research Involving Human Subjects: Guidelines for IRBs Report on Human Tissue Research (2002) Report on Human-Animal Combinations in Stem-Cell Research (2010) Report on Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning (2002) Report on Donation of Human Eggs for Research (2008)

Source: Office for Human Research Protections, U.S. Department of Health and Human Services (2013)

While the five jurisdictions employ different regulatory mechanisms to control the use of human embryos in research, they all generally provide relatively permissive environments for stem cell research.<sup>21</sup> All countries except the USA have specific legislation that prohibits the use of human cloning techniques for reproductive purposes. Australia and the UK have formal licensing systems in place that allows the creation of cloned human embryos and destruction of embryos surplus to infertility treatments for research purposes. This research may also be conducted in Japan and Singapore, at least theoretically, with approval from the relevant authorities. Human embryonic stem cell (ESC) research in the USA is controlled indirectly through restrictions placed on funding granted through the National Institutes of Health (NIH). These restrictions were recently relaxed<sup>22</sup> but, in any case, do not apply to research conducted without federal funds.

In addition, all five countries have established regulatory frameworks for the sale of medicinal drugs and governance of medical practice. As the following analysis indicates, there are technical differences in how these regulations are implemented. However, there are also broad similarities with the general approach taken in each jurisdiction that do not lead to simple explanations as to why the use of autologous ASCs appears more prevalent in some countries and not others. In the following, we describe these regulations focusing on provisions specific to autologous uses of ASCs within both formal clinical trials and the practice of medicine.

## United States

In the USA, the Food and Drug Administration (FDA) has jurisdiction over medicinal drugs, devices and biologics that are entered into *interstate commerce*, meaning that products (or products composed of ingredients) that are shipped interstate fall under the federal regulatory authority.<sup>23</sup> The FDA controls entry of these products into the market through requirements for premarket testing of safety and efficacy in specified indications, which usually involves a series of registered multiphase (I–III) clinical trials that are conducted after the sponsor obtains an Investigational New Drug (IND) designation. Subsequent market authorisation may include additional requirements for post-market surveillance.

Regulation of CTPs is administered by the Center for Biologics Evaluation and Research (CBER) Office of Cellular, Tissue, and Gene Therapies (OCTGT) within the FDA, and depending on their specific formulation, may be classified as devices, drugs, and/or biologics. CTPs are then subdivided according to criteria set out in the Code of Federal Regulations (CFR) that are intended to establish whether the product is: 1) more than minimally manipulated;<sup>24</sup> 2) intended for non-homologous use; 3) combined with other articles; or, 4) if not for autologous use, either exerts systemic effects or relies on metabolic activity.<sup>25</sup> If a CTP meets any of these definitions, it is categorized under section

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<sup>21</sup> Donald Chalmers, "Stem Cell Technology: From Research Regulation to Clinical Applications," in *Contested Cells: Global Perspectives on the Stem Cell Debate*, ed. Benjamin Capps and Alistair Campbell (London: Imperial College Press, 2010).

<sup>22</sup> Constance Holden, "A First Step in Relaxing Restrictions on Stem Cell Research," *Science* 323, no. 5920 (2009).

<sup>23</sup> Compliance Policy Guides Section 100.200 FDA Jurisdiction Over Products Composed of Interstate Ingredients

<sup>24</sup> Defined as "processing that does not alter the relevant biological characteristics of cells" in 21 CFR 1271.3(f)(2), revised 2012

<sup>25</sup> 21 CFR 1271.10 a(1-4)



351 of the Public Health Services (PHS) Act (1944) and regulated as a biological drug according to the CFR. This categorisation requires pre-market authorisation from CBER and compliance with Good Manufacturing Practices (GMPs). However, CTPs that do not meet any of these definitions are regulated solely under Section 361 of the PHS Act as “361 products”, which do not require the pre-market evaluation required for 351 products.

While the processing of 361 products should comply with Current Good Tissue Practice (CGTP) standards intended to prevent contamination by the spread of communicable diseases,<sup>26</sup> their use within clinical contexts, along with ‘off-label’ uses of approved 351 products, constitutes a medical procedure that lies outside the FDA’s jurisdiction. Medical procedures are instead governed within the practice of medicine by medical boards and civil statutes in each of the 50 American states. In 2012, the Texas Medical Board introduced rules on the investigational use of human stem cells that appears to provide an alternative to the IND pathway by allowing physicians to seek IRB approval to prescribe agents not approved by the FDA in their practice.<sup>27</sup> Despite these rules, federal laws pertaining to manufacturing standards supersede state laws and they are unlikely to provide protection against legal action taken by the FDA in asserting its authority over CTPs that fall within its jurisdiction.

Indeed, the FDA has exerted its authority over the manufacturing of autologous ASCs processed on-site for non-homologous uses in the District Court of Columbia, which broadly upheld the FDA’s interpretation of CTPs that are entered into interstate commerce as defined in CFR 1271.<sup>28</sup> The FDA has also issued a warning letter to a storage facility in Texas over violations of GMP standards for adipose-derived stem cells. In addition, the Federal Bureau of Investigation has successfully prosecuted the owner of laboratory in Arizona for unlawfully introducing allogeneic cord blood cells into interstate commerce while investigations into other related cases of mail fraud involving stem cells continue.<sup>29</sup> Civil action has also been initiated against the American subsidiary of RNL Bio, RNL Biostar, for allegedly providing misleading information about the efficacy of their autologous ASC product.<sup>30</sup> The outcomes of these lawsuits, and their impact on the availability of ASCs outside clinical trials, remain to be seen.

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<sup>26</sup> Center for Biologics Evaluation and Research (2011). Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS). Available at <http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm285223.pdf> Accessed June 4, 2013.

<sup>27</sup> Texas Medical Board Rules 22 TAC §§198.1–198.3, available online at [http://www.tmb.state.tx.us/rules/docs/Board\\_Rules\\_Effective\\_07\\_04-and-08\\_2012.pdf](http://www.tmb.state.tx.us/rules/docs/Board_Rules_Effective_07_04-and-08_2012.pdf). Accessed 18 June 2013.

<sup>28</sup> A number of key issues addressed in this case included the extension of the definition of “drug” to include cellular products, procedural issues surrounding the inclusion of autologous cells within the scope of 351 products, and whether the transplantation of autologous cells that are processed onsite can be construed as interstate commerce. While the Court found in favour of the FDA, the case remains under appeal. See *United States of America v. Regenerative Sciences, LLC et al.*, Civil Action No. 2010-1327 (RMC) US District Court DC (2012).

<sup>29</sup> Ewen Callaway, "American Scientist Arrested in Stem-Cell Clinic Sting," Nature News Blog, <http://blogs.nature.com/news/2011/12/american-scientist-arrested-in-stem-cell-clinic-sting.html>.

<sup>30</sup> David Cyranoski, "Patients Seek Stem-Cell Compensation," Nature News Blog, <http://blogs.nature.com/news/2012/07/patients-seek-stem-cell-compensation.html>.

## Japan

Japan has a pre-market evaluation process for drugs and devices that is similar to the US FDA system. In such cases, market approval is generally provided by the Ministry of Health, Labour and Welfare (MHLW) under powers conferred by the *Pharmaceutical Affairs Law (PAL)* following the evaluation of data from clinical trials that demonstrates safety and efficacy. While the MHLW can, and sometimes does, conduct the review for approving clinical trials and granting marketing approval, the Pharmaceuticals and Medical Device Agency (PMDA) – an administrative agency established under the MHLW – usually carries out this function.<sup>31</sup> In practice, requests and notifications are generally submitted to the PMDA, which reviews the submission and reports its opinion to MHLW, which either grants approval or makes further recommendations.

Under the PAL, CTPs may be classified as ‘drugs’ if their action is pharmacological or ‘devices’ if their action is structural or physical. However, only those derived from *processed* human cells and tissues are regulated under the PAL. This includes CTPs that are expanded *ex-vivo*, treated pharmacologically for activation, biologically-altered, combined with scaffolds or genetically modified.<sup>32</sup> By contrast, unprocessed CTPs<sup>33</sup> are not regulated under the PAL. Their use presumably falls within the practice of medicine, which is regulated by the Medical Practitioners Law (MPL) (1948).<sup>34</sup>

The MPL, which the MHLW also administers, considers a practitioners’ act of producing an unapproved drug and administering it to a patient as falling within the scope of ‘physician discretion’ in medical practice. CTPs that are administered in this context are therefore not governed by the PAL,<sup>35</sup> and practitioners need not seek prior approval from the MHLW/PMDA when acting within this zone of discretion. If the CTP is being administered in the context of clinical research, as distinguished from a clinical trial (*chiken*), then practitioners are expected only to observe the *2003 Ethical Guideline on Clinical Research*, and if using stem cells, the *Guidelines on Clinical Research Using Human Stem Cells (2006 Guidelines)* will also apply. These Guidelines apply to any research using stem cells, including autologous ASCs, conducted outside the formal PAL clinical trial framework.<sup>36</sup> Such studies are subject to the same evaluation for safety and ethical requirements as a formal clinical trial, except that it is the MHLW rather than the PMDA that conducts the review.

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<sup>31</sup> Article 14.2., paragraph 1 and Article 80.3., paragraph 1, Pharmaceutical Affairs Law

<sup>32</sup> Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue (PFSB/MHLW Notifications, 2008.

<sup>33</sup> *Ibid.* Includes the separation of tissue, mincing of tissue, separation of cells, isolation of specified cells, treatment by antibiotics, rinsing, sterilisation by gamma-rays etc., freezing and thawing.

<sup>34</sup> Act No. 201 of 1948.

<sup>35</sup> Article 17, Medical Practitioners Law.

<sup>36</sup> They do not apply to the PAL clinical trials. Paragraph 3, Scope: The present guidelines cover human stem cell clinical research intended to study the transplantation or administration of human stem cells, etc. into the human body for the treatment of medical conditions outlined in Chapter 4. However the following cases are not covered by these guidelines: (1) General medical practices of established safety and efficacy. (2) Clinical trials conducted under the Pharmaceutical Affairs Law (1960 Law 145).

Although research using stem cells that are obtained by 'minimal manipulation' are excluded from these Guidelines and thus do not require approval from the MHLW.<sup>37</sup>

In addition, the MHLW has issued the *Practice Notice: Regarding the Practice of Regenerative and Cell Therapy with Autologous Cells and Tissue in Medical Institutions (2010)*. According to this Notice, medical institutions that intend to implement medicines using autologous stem cells need only seek approval from an IRB. Interventions that are classified as advanced medical therapy, which excludes cosmetic and preventative medicines, should advance into clinical trials for regulatory approval and application of insurance. However, administrative guidance documents such as this do not have the force of law, and compliance is merely voluntary.

On 20 November, 2013, the Japanese Diet enacted the *Regenerative Medicine Law (2013)* along with revisions to the PAL. These new laws aim to simplify and speed-up the approval process for new regenerative medicine products, particularly stem cells. Sponsors of CTPs will now be able to receive marketing approval after providing only limited data regarding safety and efficacy, and without the need to conduct three phases of formal clinical trials. Post-marketing surveillance will then be conducted for between five and seven years to further evaluate a product's safety and efficacy.<sup>38</sup> In addition, companies will be permitted to use data from clinical research conducted at medical institutions to demonstrate the safety of their products.<sup>39</sup> It is not yet clear if or how these reforms will affect the operation of the MPL.

## Australia

In Australia, CTPs are regulated federally by the Therapeutic Goods Administration (TGA) under the *Therapeutic Goods Act (1989)* according to a recently implemented framework for biologics.<sup>40</sup> This framework categorises CTPs as either being: 1) regulated as therapeutic goods, but not as biological goods; 2) regulated as biological goods under the biologics framework; and 3) not regulated as biological goods (excluded from regulation).<sup>41</sup> The first category includes biological prescription medicines, such as vaccines, blood, plasma derivatives, and cryopreserved haematopoietic progenitor cells that are used for haematopoietic reconstitution. These products are listed as medicinal products on the Australian Register of Therapeutic Goods (ARTG) following pre-marketing assessments of safety and efficacy in clinical trials in a manner broadly similar to the approval processes for drugs in the USA and Japan.

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<sup>37</sup> 'Minimal manipulation' is defined as the "manipulation of cells in ways that do not affect their inherent biological properties, such as tissue isolation, tissue sectioning, isolation of human stem cells or differentiated cells, treatment with antibiotics, washing, sterilization by gamma rays or other means, freezing and thawing". Stem cells collected from human fetuses (including dead fetuses) are also not covered under these Guidelines. In addition, the 2006 Guidelines state that human embryonic stem cells shall not be used in clinical research until such standards have been established for the clinical research use of human embryos.

<sup>38</sup> D. Cyranoski, "Japan to offer fast-track approval path for stem cell therapies," *Nature Medicine* 19, 510 (2013).

<sup>39</sup> Y. Kobayashi, "Regenerative medicine firms to benefit from new rules," *Yomiuri Shimbun* May 30, 2013.

<sup>40</sup> A. E. Trickett and D. M. Wall, "Regulation of Cellular Therapy in Australia," *Pathology* 43, no. 6 (2011).

<sup>41</sup> Part 3-2A of the *Therapeutic Goods Act 1989* defines biologics as "a thing made from, or that contains, human cells or human tissues and that is used to treat or prevent disease, ailment, defect or injury; diagnose a condition of a person; alter the physiological processes of a person; test the susceptibility of a person to disease; or replace or modify a person's body parts"

The second category of products are regulated as biologics and include human stem cells, tissue-based products, such as skin and bone, genetically modified and *in vitro* expanded cell-based products, and combined cell and tissue products. These products are classified according to a risk-based framework detailed in the *Australian Regulatory Guidelines for Biologicals*, which applies oversight measures based on the degree of manipulation or alteration, and the intended use (non/homogeneous, autologous/allogeneic) of the CTPs. These four classes are summarised in Figure 1.

**Figure 1: Four Classes of Biological Products Regulated by the Australian TGA**

Class	Risk	Description	Requirements
1	Very Low	Products manufactured under medical supervision	A statement of compliance & entry on ATGR but product dossier
2	Low	Minimally manipulated, homologous use	Entry on ATGR, GMP compliance and product dossier
3	Medium	More than minimally manipulated, non/homologous use	Same as Class 2, but product dossier must include safety & efficacy data
4	High	Highly manipulated, non/homologous use	Same as Class 3 with highest level of safety & efficacy assessment

All CPTs regulated as biologics under this framework must be entered onto the ARTG following a pre-market approval process, although assessments of safety and efficacy data only apply to products that are more than minimally manipulated in Classes 3 and 4. Manufacturers of products in Classes 2, 3, & 4 must also obtain a license from the TGA that demonstrates compliance with principles equivalent to the *Australian Code of Good Manufacturing Practice (GMP) for human blood and tissues*. Very low risk products in Class 1 require only a statement of compliance with these standards. At the time of writing, no products had been listed in this class.

Products exempt from both of these categories are not regulated as biological or therapeutic goods. Under the *Therapeutic Goods (Excluded Goods) Order No. 1 of 2011*, these products include fresh viable human organs and haematopoietic progenitor cells for the purpose of haematopoietic reconstitution, reproductive tissue for use in assisted reproductive therapy, and most controversially, CTPs that are collected from a patient who is under the clinical care and treatment of a registered medical practitioner, and manufactured by that practitioner, or under the professional supervision of that practitioner. In this case, the CTPs must be used in the treatment of a “single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner”.<sup>42</sup>

The TGA has provided additional guidance of the exclusion order, which specifies that the CTPs must be for autologous use, that a single medical practitioner must assume responsibility for the clinical care of that patient, and where the practitioner is not directly involved in the manufacture of the CTP, that there be a “specified relationship with the agent/agency that meets the requirements for professional supervision.”<sup>43</sup> The use of CTPs that are excluded from TGA regulation would thus fall within under the jurisdiction of the Medical Board of Australia and practitioners would have to

<sup>42</sup> Section 4q, *Therapeutic Goods (Excluded Goods) Order No. 1 of 2011*

<sup>43</sup> Excluded Goods Order No. 1 of 2011: Guideline for Items 4(o), 4(p), 4(q) and 4(r)

comply with guidance contained in the *Good Medical Practice: A Code of Conduct for Doctors in Australia*. Practitioners are also required to observe federal laws pertaining to the use of advertising, as breaches may incur prosecution from the Australian Health Practitioner Regulation Agency (AHPRA). No such prosecutions have been reported for offenses relating to misleading or deceptive advertisements of CTPs in Australia.

## Singapore

Singapore does not have specific legislation to regulate CTPs, although they broadly fall within the scope of *The Medicines Act* (1975, revised 1985). This Act provides laws for the manufacturing, distribution and marketing of medicinal products, defined as “any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, imported or exported for use wholly or mainly [...] for a medicinal purpose”.<sup>44</sup> CTPs are not explicitly included in this definition, but nor are biologics, which the Health Sciences Authority (HSA) defines in its guidance for registering medicinal products, as “products derived from biological systems”, including whole cells or organisms, or parts thereof.<sup>45</sup> Manufactures of unlicensed products that fall within this definition are required to apply for a New Drug Application through the HSA, similar to an IND in the US, which is assessed following the submission of clinical documents demonstrating safety and efficacy, according to the *Medicines (Clinical Trials) Regulations* (1978, revised 2000).

The Medicines Act provides for exceptions to these regulations. Restrictions on the sale, supply and manufacturing of medicinal products that are set out in Act do not apply to “the preparation, dispensing and assembly of any medicinal product by or under the supervision of a practitioner for the purpose of administration to a patient or animal under his care”<sup>46</sup>. Thus, as biological medicinal products, the Act would not apply to the manufacturing, sale or use of CTPs within hospitals and medical clinics. The Act also “does not apply to products categorised and regulated as health products under the Health Products Act.”<sup>47</sup> Currently though, the *Health Products Act* (2007) only regulates product categories that have been specified in the First Schedule, which is thus far limited to medical devices and cosmetic products,<sup>48</sup> and do not include CTPs.<sup>49</sup>

The HSA has proposed to add CTPs to the First Schedule and are currently drafting regulations to regulate CTPs as health products. The proposed framework resembles the risk-based classification system used in Australia.<sup>50</sup> If adopted in Singapore, it is unclear how CTPs may be used in hospitals as the Health Products Act does not include exemptions for products that are manufactured by or

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<sup>44</sup> *Medicines Act* (1975) Part 1 Section 3(1)

<sup>45</sup> *Guidance on Medicinal Product Registration in Singapore* (2011)

<sup>46</sup> *Medicines Act* (1975) Part 2 Section 7(4)

<sup>47</sup> *Medicines Act* (1975) Part 7 Section (77)

<sup>48</sup> *Health Products Act* (2007) Part 1 Section 4(1)

<sup>49</sup> Medical devices are defined in the Schedule as “any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article” and cosmetic products are “any substance or preparation that is intended by its manufacturer to be placed in contact with the various external parts of the human body or with the teeth or the mucous membranes of the oral cavity”. Thus, while a point-of-care cell processing device may fall within the scope of the Act, the cells processed using this technology would not.

<sup>50</sup> Ong, L.L. (2013), Regulation of human cell- and tissue-based therapeutic products in Singapore. Presented to the *Regulatory Session I: Regulations Around the World* at the 19th International Society for Cell Therapy Annual Meeting in Auckland, New Zealand 22-25 April 2013.

under the supervision of medical practitioners. CTPs that are processed and stored for human transplantation in hospitals and medical clinics are covered under the *Guidelines for Healthcare Institutions Providing Tissue Banking* (2003).<sup>51</sup> This guidance includes “all constituent parts of the human body, including surgical residues” but excludes solid organs, placenta, blood and blood products, and reproductive tissues,<sup>52</sup> and does not include tissues that have been “processed in such a manner that their functional, structural and biological characteristics have been altered”.<sup>53</sup> These products are classified as biologics, which currently fall under the Medicines Act.

The legal ambiguity may have encouraged a small number of physicians to market stem cells in Singapore without prior approval from the HSA. While these physicians had not clearly broken any laws, the Singapore Medical Council (SMC) has taken disciplinary action against three practitioners offering CTPs outside clinical trials: Drs Georgia Lee and Low Chai Ling in 2007, for offering aesthetic treatments with stem cell ‘extracts’ without evidence of efficacy;<sup>54</sup> Dr Martin Huang Hsiang Shui in 2009, for offering therapies involving the injection of xenogenic (animal) foetal cells into patients for anti-ageing and rejuvenation purposes;<sup>55</sup> and Dr Wong Yoke Meng in 2010, for offering stem cell-based ‘anti-aging’ products and therapies that were not medically proven.<sup>56</sup> All three doctors were charged with professional misconduct, issued with fines and censured, but not removed from the medical register. However, in 2012, the Singapore Court of Appeals overturned the SMC’s verdict against Dr Low on grounds that there were no established or official standards for the practice of aesthetic medicine at the time of the Discipline Committee’s inquiry to substantiate a charge of professional misconduct.<sup>57</sup> No claims have surfaced around the use of autologous ASCs.

## United Kingdom

The UK has also adopted a risk-based approach although it differs slightly from the other jurisdictions; partly due to its status within the European Union. In EU countries such as the UK, CTPs are regulated as ‘advanced therapy medicinal products’ (ATPM) under a national framework that integrates the regulations and directives of the European Commission: this includes the Tissue Framework Directive (2004/23/EC), the ATPM Regulation (EC No 1394/2007) and the ATPM Directive (2001/83/EC). According to ATPM Regulation, a centralised authorisation procedure applies to ATPMs that are intended to be marketed within the European Union. This procedure requires approval from the European Medicines Agency (EMA) following review of the safety and efficacy data. This data is initially reviewed by the EMA’s Committee for Advanced Therapies (CAT), which has the discretion to determine the extent and quality of the non-clinical and clinical data to be included in the marketing authorisation application as well as conduct of follow-up efficacy,

<sup>51</sup> Regulation 4 of the *Private Hospitals and Medical Clinics Regulations* (1991, amended 2002)

<sup>52</sup> *Guidelines for Healthcare Institutions Providing Tissue Banking* (2003) Section 1.1a

<sup>53</sup> *Guidelines for Healthcare Institutions Providing Tissue Banking* (2003) Section 1.1b

<sup>54</sup> *Low Chia Ling v Singapore Medical Council* (2012) SGHC 191 High Court Originating Summons No 18 of 2012.

<sup>55</sup> Singapore Medical Council (2009), Disciplinary Inquiry Against Dr Martin Huang Hsiang Shui. August 2009.

<sup>56</sup> Singapore Medical Council (2010), Disciplinary Inquiry Against Dr Wong Yoke Meng. September 2010.

<sup>57</sup> *Low Chai Ling v Singapore Medical Council* (2012) SGHC 191 High Court Originating Summons No 18 of 2012. The SMC has since withdrawn the charges against the owner of clinic in question, Dr Lee and her employee Dr Low.

pharmacovigilance and risk-management systems.<sup>58</sup> The CAT then makes recommendations to the Committee for Medicinal Products for Human Use (CHMP) for final approval.

The supervisory authority for UK manufacturers or importers of centrally authorised ATMPs is the Medicines and Healthcare Products Regulatory Agency (MHRA). The MHRA defines CTPs according to the ATMP Directive, which may be classified as a gene therapy product, a somatic cell therapy product and/or an engineered tissue product.<sup>59</sup> However, the classification of somatic cell therapies only includes products that are substantially manipulated for use in the treatment, prevention or diagnosis of a disease through the “pharmacological, immunological or metabolic action of its cells or tissues”.<sup>60</sup> Thus, ASCs that are not substantially manipulated are excluded from the ATMP Regulations,<sup>61</sup> and if used an autologous graft “within the same surgical procedure and without being subjected to any banking process”, are also excluded from regulation under the Tissue Framework Directive.<sup>62</sup> Further exemptions are provided under ‘Hospital Use’ scheme of the ATMP Directive, which allows for the ‘non-routine’ use of any ATMP for an individual patient<sup>63</sup>.

Similar to Singapore, the Medicines Act (1968) provides additional exceptions for medicinal products that are manufactured under the supervision of a registered medical practitioner.<sup>64</sup> The UK framework also provides a ‘specials’ scheme, which allows for the manufacture and importation of unlicensed medicinal products.<sup>65</sup> The purpose of this scheme is to ensure that patients are able to access medicines that the MHRA has not approved for marketing. Thus, with permission of the MHRA, holders of a specials license may supply an unapproved CTP to practitioners and pharmacies regardless of their intended use, although the procurement and processing of such products may still fall under purview of the Tissues Framework Directive and the prescribing physician must conform to accepted ethical standards which place the interests of patients before commercial imperatives.<sup>66</sup>

Outside the formal regulatory framework for CTPs, the conduct of registered practitioners in the UK is governed under the practice codes and guidelines of the British General Medical Council (GMC). Empowered under the *Medical Act 1983*, the GMC has the authority to place sanctions on practitioners and remove those from the register who’s fitness to practice is found to be impaired. In

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<sup>58</sup> Committee for Advanced Therapies. Overview EC No 1394/2007. Available at [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000126.jsp&mid=WC0b01ac05800292a5](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000126.jsp&mid=WC0b01ac05800292a5) Accessed 19 June 2013.

<sup>59</sup> Directive 2001/83/EC

<sup>60</sup> *Ibid* Part 4 Paragraph 2.2

<sup>61</sup> Non-substantial manipulation includes cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation and vitrification. EC Regulation No 1394/2007 Annex I

<sup>62</sup> Directive 2004/23/EC Paragraph 8

<sup>63</sup> ATMP Directive 2001/83/EC Article 3(7)

<sup>64</sup> The Medicines Act 1968 Section 9(1)

<sup>65</sup> As enabled under the Medicines Act 1968 and the Human Medicines Regulations 2012 [SI 2012/1916]. Specific guidance for this scheme is currently under review.

<sup>66</sup> Department of Health (2010). Trading Medicines for Human Use: Shortages and Supply Chain Obligations. Available at [http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/documents/digitalasset/dh\\_123637.pdf](http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_123637.pdf) Accessed 19 June 2013.

2010, the GMC deregistered Dr Robert Trossel following an investigation by the Fitness to Practice Panel for unjustifiably administering an allogeneic cellular preparation (also found to contain bovine neural cells) to patients affected by multiple sclerosis at a clinic in Rotterdam.<sup>67</sup> The Panel stated that the interventions were based on “anecdotal and aspirational information”, and called his actions “unjustifiable” and “exploitative”, and “repeated and serious” breaches of many of the “essential tenets” of good medical practice. However, no investigations have been initiated against practitioners prescribing autologous ASCs outside of the accepted standard of care.

## DISCUSSION

Subtle differences can be seen in both the technical language and structure of the regulatory instruments that govern experimental and clinical uses of CTPs in the five jurisdictions examined. Yet, the general approach is the same: each country is attempting to regulate clinical practice so that it is evidence-based and works in the best interests of both the nation and the people who require care. At the same time, the regulations still aim to provide sufficient clinical freedom such that innovation can be pursued by clinicians and researchers, and that interventions that lack the level of evidence necessary for licensing or subsidization may still be accessible to patients – particularly those with life-threatening illness and with few other therapeutic options. While these are laudable aims and the approach may support research, it also creates a number regulatory weaknesses or loopholes that may be exploited by commercial interests and transnational bionetworks.

### Structural Weaknesses in the Regulation of Research and Practice with CTPs

Each of the countries examined in our analysis attempt to provide a clear evidence-based pathway for CTPs that are regulated as medicinal drugs while allowing patients to access low-risk interventions with autologous ASCs under the supervision of their treating physicians. This general approach is designed to provide the necessary protections for research subjects while maintaining professional and patient autonomy. To support this goal, all five jurisdictions have implemented, or planning to in the case of Singapore, a risk-based approach to the regulation of CTPs. This approach gives regulators some flexibility in determining the level of oversight and standards of evidence that should apply before these products are introduced into clinical settings.

Autologous ASCs that are sourced from an individual patient and transplanted back into that patient are generally regarded as representing a relatively lower risk than allogeneic products. Details about the level of manipulation and intended use of the cells vary slightly across jurisdiction, but there is a general consensus that these products do not pose serious safety threats and are subject to relatively limited regulatory oversight. Where cells are highly manipulated and there is less certainty about the potential risks to patients, and regulatory requirements impose greater oversight before they are introduced into the wider market. These cells are also treated as biological drugs and sponsors are required to obtain an investigational license and demonstrate evidence of safety and efficacy in registered clinical trials.

Yet, even in these instances, there is regulatory flexibility and patients may have access to CTPs that have not been approved for marketing. All jurisdictions have special programs that allow patients in exceptional circumstances to access unapproved medicinal drugs. The programs differ in name

<sup>67</sup> Fitness to Practice Panel; 11 January-5 March 2010; 27 March 2010; 10-11 April 2010; 6 – 10 & 27 – 29 September 2010; Regent’s Place, 350 Euston Road, London, NW1 3JN; Name of Respondent Doctor: Dr Robert Theodore Henri Kees Trossel. (Accessed 6 May 2013, at <http://www.casewatch.org/foreign/trossel/sanction.pdf>)



slightly and some of the conditions vary (for example, in the USA, the experimental agent must be the subject of an active IND, and in Japan the drug must be approved in the exporting country, whereas there are no such restrictions in Australia and the UK<sup>68</sup>), but the basic premise is the same – to ensure that patients can access drugs that might save or significantly improve their quality of life on compassionate or humanitarian grounds. This same premise applies in principle to autologous ASCs. Europe, for example, has already enabled transplantation of artificial tracheas engineered from the stem cells of patients outside clinical trials with special permissions from the regulators.<sup>69</sup>

Further to these exceptional circumstances, all of the jurisdictions (excluding the USA) have laws that explicitly allow the manufacture of any medicinal drug, including biologics, under the supervision of a registered practitioner within hospitals, by licensed external vendors or imported internationally for local uses. In the USA, the manufacturing of medicinal drugs, including CTPs, is controlled where products, or the ingredients that made up those products, are shipped across interstate borders. The FDA's authority over CTPs made with ingredients sourced entirely within state borders is unclear.<sup>70</sup> The United States, therefore, appears to be the most strictly regulated jurisdiction, despite the reports of physicians prescribing autologous ASCs that the FDA has not approved for marketing.

In considering how these discrepant practices occur, it is important to realize that *medical procedures* fall within the practice of medicine, which is regulated under separate governance frameworks in all jurisdictions. Thus, the act of prescribing a registered drug or CTP for indications that have not been approved (i.e. 'off-license or 'off-label') falls outside of the jurisdiction of the regulatory authorities. While practitioners, healthcare institutions or manufacturers are not permitted to market or advertise the drug or CTP for any indication that has not received pre-market approval, physicians may lawfully prescribe them within the discretion of their professional judgment. Where interventions do not fall within the accepted standard of care, then practitioners generally need adequate justification and may require special permission from an institutions' clinical practice, clinical governance or ethics board. In contrast, if interventions are prescribed as part of a research protocol, then they will generally need to be approved by an IRB (except in the US, where the Common Rule is only mandated for research supported with federal funds). However, no permission or oversight is required from the authorities that regulate the marketing of medicinal products in any of these jurisdictions.

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<sup>68</sup> See the Expanded Access Program in the US at <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.htm>; the Named Patients Access program in Japan; the Special Access Scheme in Australia at <http://www.tga.gov.au/hp/access-sas.htm>; the UK Specials Scheme at <http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedalicence/Medicineshatdonotneedalicence/index.htm> and the Hospital Exemption Scheme at <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>. Singapore does not have a formal program, but the regulator has the discretion to apply similar arrangements; see [http://www.hsa.gov.sg/publish/hsaportal/en/health\\_products\\_regulation/safety\\_information/product\\_safety\\_alerts/2008/update\\_on\\_aprotinin.html](http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/2008/update_on_aprotinin.html)

<sup>69</sup> Anthony P Hollander, "A Case Study of Experimental Stem Cell Therapy and the Risks of over-Regulation," in *Contested Cells: Global Perspectives on the Stem Cell Debate*, ed. Benjamin Capps and Alistair Campbell (London: Imperial College Press, 2010).

<sup>70</sup> William T Koustas and John R Fleder, "Fda Continues Efforts to Expand Power over Intrastate Commerce," FDA Law Blog, [http://www.fdalawblog.net/fda\\_blog\\_hyman\\_phelps/2011/10/fda-continues-efforts-to-expand-power-over-intrastate-commerce.html](http://www.fdalawblog.net/fda_blog_hyman_phelps/2011/10/fda-continues-efforts-to-expand-power-over-intrastate-commerce.html).

Other medical procedures that generally fall outside the control of the regulators typically include human organ transplants, haematopoietic stem cell transplants using autologous grafts or allogeneic tissues obtained from a relative within two degrees of separation, and human reproductive tissues that are used for *in vitro* fertilisation and other artificial reproductive technologies. They also generally exclude procedures with autologous ASCs that have not been manipulated extensively or combined with other articles and are intended for use in functionally compatible tissues. There are, however, important differences in the terms used to describe low-risk products as 'minimally manipulated' or 'non-substantially manipulated'. The processes that characterize minimal or non-substantial manipulation are made explicit in Australia, the UK and Japan, while the USA uses a definition that reflects whether the basic characteristics of the cells are altered in the process. This approach provides the FDA with greater flexibility, and thus control, over CTPs that fall within its jurisdiction. However, because the definition is vague, it is more open to interpretation, and thus challenge, by practitioners who want to offer autologous ASCs without going down the IND pathway.

## CONCLUSIONS

Our analysis does not explain why autologous ASCs are being prescribed outside clinical trials more often in Australia, Japan and the US, than in Singapore and the UK. While there are technical differences and ambiguities in the language and implementation of respective regulatory instruments, the general approach in each country is the same – regulating clinical practice so that it is evidence-based while still allowing enough freedom for clinicians and research to innovate with new interventions and autonomy for patients to access low risk CTPs that lack the level of evidence necessary for marketing or subsidization from public and private health insurers. Indeed, across all five jurisdictions, regulators and policymakers are generally reluctant to interfere in decisions that many would argue should remain in the private world of the doctor and their patient; leaving the clinical space largely free from external supervision. However, while this is historically, culturally and socio-politically acceptable, few would agree that physicians should be allowed to prescribe whatever they want without being accountable to their patients or to the social and political systems that ultimately pay for the provision of their healthcare.

The challenge in implementing these risk-based approaches is that the contexts that create scientific research and clinical medicine, and the characteristics of their practices, are frequently incompatible. The standards of evidence required to conduct clinical research differ greatly from what practitioners need to make clinical decisions. Scientific methodology is characterized by uncertainty and researchers design protocols to test hypotheses that have inherently uncertain outcomes. The uncertainty that underlies this methodology provides the ethical justification for conducting clinical research in the first place. For example, clinical equipoise, or the presence of genuine uncertainty,<sup>71</sup> provides justification for randomization, and trials may be designed to terminate once an acceptable level of certainty is reached regarding the question under study. Clinicians, on the other hand, need proof, and the presence of uncertainty and disagreement within the professional community about treatment options must allow physicians the freedom to exercise clinical judgments.<sup>72</sup>

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<sup>71</sup> B Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317, no. 3 (1987).

<sup>72</sup> P B Miller and C Weijer, "Rehabilitating Equipoise," *Kennedy Institute of Ethics Journal* 13, no. 2 (2003).

Balancing the demands of research with professional and patient autonomy in regulation may thus create a potentially intractable problem. Whereas uncertainty is a key characteristic of science, and regulations, ethical guidelines and governance processes can be designed to minimize harms that may arise from it, regulating clinical decisions in the face of uncertainty is, in many ways, much more difficult. However, regulators do have power to control unethical and illicit clinical practices, and a number of mechanisms may be used to control the use of autologous ASCs outside clinical trials. All five countries have torts laws in place for medical negligence and consumer protection laws that restrict false advertising and the provision of misleading information in medical practice. The two countries that have been most successful in limiting unethical practices with autologous ASCs – the UK and Singapore – have also activated respective medical licensing boards into action against offending practitioners. Even though the practitioners in question had been offering allogeneic products, their sanctioning, and particularly the deregistration of one, Robert Trossel, would have undoubtedly sent a stern warning to other practitioners considering offering unproven interventions with any stem cell-based product outside clinical trials.

While these measures may, at least in part, explain why the prescription of autologous ASCs outside clinical trials appears less prevalent in Singapore and the UK than elsewhere, additional steps may be necessary to balance the conflicting demands of research and practice, and control unethical practices with stem cells. For a start, clearer guidance is needed for clinicians who want to prescribe low-risk interventions with autologous ASCs responsibly and access higher-risk CTPs before they have been approved for marketing. Special access schemes are already in place for these purposes, however, to whom these provisions may apply and who should have access to specific cell populations needs to be clarified. Further clarification is also needed on who should pay for interventions that have not been approved for marketing or demonstrated as safe and effective as costs for such treatments are generally not reimbursable under public or private health insurance providers. The types of skills and expertise required for the isolation and processing of cell populations, as well as the disease being targeted for treatment, are issues that should warrant further discussion.

Beyond professional guidelines, greater consistency and less ambiguity in regulatory instruments across jurisdictions is necessary because even though they provide regulators with a degree of discretion, the vagaries and inconsistencies are also open to willful misinterpretation and exploitation by unscrupulous operators. Relevant authorities should also activate existing laws and regulations that protect consumers from false advertising and the provision of misleading information in medical practice. It is crucial that the wholesale marketing of such interventions without sufficient evidence should be prosecuted under the relevant consumer protection laws and offending practitioners sanctioned by the responsible medical authority. For clinical practice cannot be regulated in the same way as research if the goal is to ensure that patients have access to novel interventions where efficacy is uncertain and that innovation can occur within clinical contexts.

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